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Regina D. McKinney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
D'Azzo *et al.*	:	Art Unit: 1652
Serial No. 09/966,893	:	Examiner: Christian l. Fronda
Filed: September 28, 2001	:	Atty Docket: SJ-01-0020
For: Targeting Proteins to Cells Expressing Mannose Receptors Via Expression in Insect Cells	:	

APPEAL BRIEF PURSUANT TO 37 C.F.R. §1.192

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

This is an Appeal from the Final Rejection of claims 8-13 of the referenced application (published on June 20, 2002 as Pub. No. 2002/0077292) dated July 1, 2003. The Examiner subsequently issued an Advisory Action dated December 2, 2003 upholding this rejection. The Notice of Appeal was filed for this application on September 5, 2003, making this Appeal Brief due on November 5, 2003. A Petition for a two-month extension of time accompanies this Appeal Brief, extending the due date for filing of this Appeal Brief to January 5, 2003.

The fees required under §1.17(c) and the required petition for extension of time for two months for filing this brief and fees therefore are addressed in the accompanying papers.

This brief is transmitted in triplicate in accordance with 37 C.F.R. §1.192(a).

I. REAL PARTY IN INTEREST

The real party in interest in this application is St. Jude Children's Research Hospital by virtue of an assignment executed by both named inventors on September 27, 2001 and recorded in the U.S. Patent Office at Reel/Frame 012248/0406 (4 pages).

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to appellant, appellant's legal representative, or assignee St. Jude Children's Research Hospital which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

There are a total of 20 claims in this application. Claims 1-7 and 14-20 have been withdrawn from consideration but not canceled. Claims 8-13 are pending and stand rejected. No claims have been allowed.

Claims 8-13 are on appeal. The claims on appeal are reproduced in their present form in the attached appendix.

IV. STATUS OF AMENDMENTS

An amendment of claim 8 was submitted September 5, 2003 in response to the Final Rejection dated July 1, 2003. In the Advisory Action dated December 2, 2003 the Examiner indicated that this amendment would not be entered upon filing of an Appeal Brief. Therefore this amendment has not been incorporated into the claims as they appear in the attached appendix.

V. SUMMARY OF INVENTION

The present invention is drawn to a pharmaceutical composition comprising a protein useful for treating a lysosomal storage disorder that is produced in an insect cell culture and a pharmaceutically acceptable carrier. The heart of the invention lies in the discovery that proteins produced in insect cells are uniquely susceptible to uptake by macrophages. Macrophages are the primary therapeutic target for proteins used in enzyme replacement therapy to treat lysosomal storage disorders. This discovery revealed that proteins useful for treating lysosomal storage disorders, when produced in insect cells, have a therapeutic advantage because they are naturally targeted for uptake by macrophages. Pharmaceutical compositions comprising protective protein/cathepsin a (PPCA) produced in insect cell culture to treat Galactosialidosis are specifically claimed.

VI. ISSUES

The following issues remain:

1) Whether claims 8-13 are properly rejected under 35 U.S.C. §112, first paragraph for containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2) Whether claims 8-13 are properly rejected under 35 U.S.C. §112, first paragraph for failure of the specification to provide an enabling disclosure for claimed compositions other than those comprising protective protein/cathepsin A (PPCA).

3) Whether claims 8-13 are properly rejected under 35 U.S.C. §102 as anticipated by International PCT Application Pub. No. WO 00/39150 naming John D. Sharp as the sole inventor (hereinafter referred to as "Sharp" consistent with the prosecution history).

VII. GROUPING OF CLAIMS

1) With respect to the written description rejection made under 35 U.S.C. §112, first paragraph, all claims on appeal do not stand or fall together. Dependent claims 9 and 10 add limitations for which additional arguments are made against this rejection and should be considered to be separate from claims 8 and 11-13 for the purpose of considering this rejection.

2) With respect to the enablement rejection made under 35 U.S.C. §112, first paragraph, all claims on appeal do not stand or fall together. Dependent claims 9 and 10 add limitations for which additional arguments are made against this rejection and should be considered to be separate from claims 8 and 11-13 for the purpose of considering this rejection.

3) With respect to the anticipation rejection made under 35 U.S.C. §102, all claims on appeal stand or fall together.

VIII. ARGUMENTS

A. The Specification Adequately Describes the Claimed Invention

Claims 8-13 stand rejected under 35 U.S.C. §112, first paragraph based on the assertion that the claims contain subject matter which was not sufficiently described in the specification.

There is a strong presumption that an adequate written description of the claimed invention is present in the specification. *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (Ct. Cust. Pat. App. 1976); *see also* Manual of Patent Examining Procedure (MPEP) Sec. 2163, page 156, col. 1. To overcome this presumption, the Examiner bears the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. *In re Wertheim,* 541 F2d at 263-264; *see also* MPEP Sec. 2163, page 158, col. 2. Appellants do not believe the Examiner has met this burden in this case for the reasons set forth below and in the responses submitted April 4 and September 5, 2003.

The claimed compositions have two basic components that need to be described to satisfy the written description requirement: (1) the protein component, and (2) the pharmaceutically acceptable carrier. The Examiner does not dispute the existence of a sufficient written description of the pharmaceutically acceptable carrier, which leaves only the protein component.

The proteins that may be included in the claimed composition are well known in the art and references to scientific literature and/or Genbank accession numbers disclosing the structure (amino acid sequence) of these proteins has been provided in the specification. *See, in particular*, Table 1 on pages 1-3 of Pub. No. 2002/0077292. This structural information can be used to create nucleic acid vectors for the expression of these proteins in any desired cell type,

including insect cells. Because the structures of these proteins are well known in the prior art, these structures do not need to be reproduced in the specification and in fact are preferably omitted according to *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986)("a patent need not teach, and preferably omits, what is well known in the art")(citing *Lindemann Machinenfabrik v. American Hoist & Derrick*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir.1984)); *see also Webster Loom Co. v. Higgins,* 105 U.S. 580, 585-586 (1882).

Appellants do not rely upon the primary structure; i.e. the amino acid sequence, of any of these proteins to impart patentability upon the claimed compositions. Instead Appellants properly rely on the knowledge of these structures to supplement the description of the novel and unobvious aspects of the invention in the specification. Recitation of the primary structure of each member of this group of proteins would be redundant to knowledge available in the prior art and is not necessary.

Since the protein component of the claimed compositions must be produced in a specific way via expression in insect cells, a description of this form of protein production may also be necessary to satisfy written description and/or enablement requirements. This is not difficult since this process, like the protein component of the invention, was also well known in the art. A description of this process, with appropriate reliance on supporting references, is provided at paragraphs 0059-0060 and in Examples 1 and 2 of the published application, Pub. No. 2002/0077292. Application of this process to proteins having a known amino acid sequence, such as the proteins encompassed by the claims, is straightforward and routine.

In the Final Rejection dated July 1, 2003 the Examiner asserted that the claims were unacceptable because they may encompass proteins that are not listed in Table 1 of the specification. This assertion certainly does not apply to claims 9 and 10 since these claims are

limited to a particular protein-disease combination listed in Table 1. Claim 10 is limited to compositions comprising protective protein/cathepsin A (PPCA) while claim 9 is limited to compositions for treating Galactosialidosis, the lysosomal storage disorder associated with PPCA deficiency. Thus the protein of the composition of dependent claims 9 and 10 is clearly listed in Table 1 of the specification near the bottom of page 2 of Pub. No. 2002/0077292.

The remaining claims on appeal encompass only those proteins useful for treating lysosomal storage disorders (LSDs) other than Fabry disease. A comprehensive list of such proteins is provided in Table 1 of the specification. No LSDs other than those listed in Table 1 are known by Appellants to exist, nor has the Examiner identified any such additional LSDs. Likewise, no proteins useful for treating LSDs other than those listed in Table 1 are known by Appellants, nor has the Examiner identified any such additional proteins.

Appellants attempted to address the Examiner's hypothetical concern that other such proteins may exist by amending claim 8 (and thus claims which depend from claim 8) to include only proteins listed in Table 1. While the Examiner refused to enter this amendment, it has become part of the prosecution record and, along with the argumentation made herein, represents the clear intent of Appellants to interpret the phrase "proteins useful for treating lysosomal storage disorders (LSDs)" in claim 8 (and claims depending from this claim) to encompass only those proteins listed in Table 1 of the specification. Through this prosecution history Appellants have exercised the right to act as their own lexicographer (*See, e.g. Finnegan Corp. v. Int'l. Trade Comm'n*, 180 F.3d 1354,1364, 51 U.S.P.Q. 2d 1001, 1008 (Fed. Cir. 1999)) to limit the scope of claim 8 in a manner that renders the Examiner's assertion moot.

In the Final Rejection the Examiner also asserted that "the specification does not provide a written description of administering any protein of any structure and function to treat any lysosomal storage disorder . . ." Final Rejection at page 2, par. 5. Appellants first note for the

record that they disagree with the accuracy of this assertion. The administration of the claimed compositions is sufficiently described, for example at paragraphs 0065-0076 of Pub. No. 2002/0077292, particularly considering the level of knowledge and skill in the art with respect to the administration of compositions of this type.

More importantly, this assertion is not relevant to the question of whether the claimed compositions are sufficiently described. The subject claims are drawn to pharmaceutical compositions comprising a protein component and a pharmaceutically acceptable carrier component. Appellants have explained how each of these components are adequately described in the specification. While the adequate description of how to use these compositions may be relevant to issues of enablement or perhaps utility, it is not relevant to the question of whether the claimed compositions are adequately described. Accordingly, this assertion does not support the present rejection and should be disregarded as irrelevant.

B. The Specification Enables Practice of the Claimed Invention

Claims 8-13 stand rejected under 35 U.S.C. §112, first paragraph based on the assertion that the claimed subject matter is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

As described above in response to the written description rejection, the present invention is based on the application of a conventional protein production process to known proteins in a straightforward manner. Therefore the production of the claimed compositions does not raise any significant enablement issues. This is apparent from the analysis of the enablement factors enumerated in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) provided in Appelant's Amendment and Response submitted April 4, 2003 to the first Office Action and incorporated herein by reference.

The Examiner has not provided any basis for disputing the ability of the skilled artisan to produce the claimed pharmaceutical compositions. Nor does the Examiner provide any basis for disputing the ability of the skilled artisan to administer such compositions by conventional techniques. Rather, this rejection appears to be based primarily on skepticism regarding whether administration of the claimed compositions will work; i.e. whether the compositions will be safe and effective for treating the identified conditions. Thus this rejection appears to be based more on concerns related to the utility of the claimed compositions when administered rather than concerns related to the ability to actually make and administer these compositions. As such the guidelines for examining applications for satisfaction of the utility requirement are applicable here and should be followed. Federal Register 66(4):1092-1099 (Jan. 5, 2001); MPEP Sec. 2107. Under these guidelines, the claimed pharmaceutical compositions have the specific, substantial and credible utility of being useful for treating lysosomal storage disorders via enzyme replacement therapy. Many of the proteins encompassed within the claimed compositions, produced by a means other than insect cell production, have already been used or are being tested in clinical trials to treat lysosomal storage disorders. See paragraphs 0010-0034 of Pub. No. 2002/0077292.

To support maintenance of this rejection, the Examiner asserts in the Final Rejection of July 1, 2003 at page 3, paragraph 2 that "[t]he amount of experimentation to make the claimed composition is enormous and undue and entails determining whether a particular disease is a lysosomal storage disorder disease, determining the etiology of the disease, and formulating a composition to treat or cure the disease."

This assertion certainly cannot apply to claims to claims 9 and 10, which apply to one particular lysosomal storage disorder (Galactosialidosis) and one particular protein (PPCA), respectively. In fact, the Examiner admitted in the paragraph bridging pages 2 and 3 of the Final

Rejection dated July 1, 2003 that the specification is "enabling for composition comprising a protective protein/cathepsin A (PPCA) protein useful for treating Galactosialidosis." In view of this admission, it is unclear why the Examiner has sustained this rejection against claims 9 and 10.

The scope of the remaining claims is limited to proteins listed in Table 1 of the specification as explained above in section VIII-A in the rebuttal to the written description rejection. These proteins are clearly associated with the lysosomal storage disorder they can be used to treat in Table 1. Therefore practice of the claims does not entail determining whether a particular disease is a lysosomal storage disorder and determining the etiology of the disease. This information is known and is provided in Table 1. As for formulating a composition to treat or cure the known protein deficiency for each lysosomal storage disorder, the specification clearly teaches the production of proteins in insect cells and formulation of compositions comprising such proteins using conventional techniques.

The Examiner further asserts that "[t]he specification does not teach any one particular protein/enzyme can be used to treat every lysosomal storage disorder as encompassed by the claims." Final Rejection of July 1, 2003 at page 3, paragraph 2. Appellants have agreed that the specification does not provide such a teaching. Instead the specification teaches the specific protein deficiencies associated with each particular lysosomal storage disorder, thus revealing the protein(s) which can be made into a pharmaceutical composition according to the teachings of the specification to remedy the protein deficiency characteristic of that particular lysosomal storage disorder.

Appellants do not agree that the claims encompass a single protein/enzyme for treating every lysosomal disorder and do not understand how the claims have been interpreted in this manner, particularly in light of the teachings in the specification. Rather the claims, read in light

of the specification clearly cover, for example, the use of a composition comprising acid α-1,4 glucosidase and acid α-1,6 glucosidase in enzyme replacement therapy to treat Pompe Disease, the use of β-galactosidase to treat GM1 Gangliodsidosis, etc. (see Table 1).

The claimed pharmaceutical compositions are contemplated for the same therapeutic uses as contemplated in the prior art for these same proteins produced by other methods. These compositions are made using conventional insect cell expression techniques as applied to known proteins and are fully enabled.

C. The Claimed Invention is Not Anticipated

Claims 8-13 stand rejected under 35 U.S.C. §102(a) based on the assertion that the claimed subject matter is anticipated by Sharp, J.D., International Application No. PCT/US99/31158, published as WO 00/31950 ("Sharp"). Sharp is cited by the Examiner for disclosing a PPCA polypeptide, identified therein as TANGO 176, and pharmaceutical compositions containing this polypeptide.

Sharp is NOT asserted by the Examiner to teach a pharmaceutical composition for treating Galactosialidosis comprising a PPCA polypeptide produced in an insect cell culture. Instead, the Examiner contends that such a teaching is not necessary to anticipate the claimed invention. According to the Examiner, such a teaching is not necessary because the claims do not recite the properties associated with proteins produced in insect cells that distinguish them from proteins produced by other means. The assertion that the unique properties of a product must be recited in the body of a product by process claim in order for those properties to be considered in determining patentability over the prior art is wrong.

The patentability of product by process claims over the prior art is dependent upon the presence or absence of distinguishing characteristics and properties of the product produced by

the recited process, and not upon the patentability of the recited process. *In re Pilkington*, 411 F2d 1345; 162 U.S.P.Q. 145 (C.C.P.A. 1969); *see also In re Thorpe*, 777 F.2d 695, 697, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985); *see also* MPEP Section 2113. However, there is no requirement to recite distinguishing characteristics and properties in a product by process claim in order for these to be taken into account when considering patentability over the prior art.

In fact, a major reason for using the product by process claim format is to avoid the need for such a recitation where such would be difficult. As noted in *In re Pilkington,* 411 F2d at 1349-1350 when addressing the issue of patentability of the subject invention over the prior art and appropriateness of the product by process claim format:

> "While we are satisfied that the references of record do not anticipate appellant's glass or demonstrate that it would be obvious, the differences between that glass and the glass of the prior art do not appear to us to be particularly susceptible to definition by the conventional recitation of properties or structure.[5] Under the circumstances, it seems to us that the present product-by-process claim satisfies the requirements of 35 U.S.C. §112 and is appropriate here."

In this case Appellants have described, to the extent possible, the unique character of proteins produced in insect cells regarding post translational modifications, particularly with respect to their glycosylation pattern and more particularly with respect to exposed mannose residues (see, e.g., Appellant's specification, Pub. No. 2002/0077292 at paragraphs 0007 and 0061). The fact that proteins produced in insect cell culture have unique attributes relative to proteins produced by other means is not a new concept, but these unique characteristics do not easily fit into the form of a claim limitation. Appellants therefore chose to use the product by process claim format that is designed for this sort of situation.

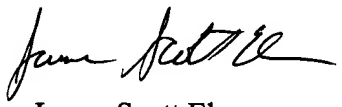
It is not disputed that the unique characteristics of proteins produced in insect culture clearly distinguish them from proteins produced by other known means. Therefore if one takes these unique characteristics into account, it is clear that the Sharp disclosure does not anticipate the claimed invention.

Appellants note for the record here that Sharp does generically mention the production of proteins in insect cells when providing a laundry list of the various forms of standard expression vectors and host cells that may be used to produce proteins (see Sharp at pages 65-72, particularly 66-67). However, Sharp does not specifically teach the production of PPCA (i.e TANGO 176) in insect cell culture for the purpose of making a pharmaceutical composition useful for treating Galactosialidosis. Nor can such a teaching be inferred considering the state of the art at the time of the Sharp disclosure. In this regard, the background section of Appellant's application notes that "post-translational modifications in insect cells are not identical to those that occur in mammalian cells, and these differences are not completely understood. [citations omitted] These differences and their ill-defined nature are generally considered a disadvantage of producing proteins in insect cells.[citations omitted]" Pub. No. 2002/0077292 at paragraph 0007. These observations were valid when this application was filed on September 28, 2001 and were certainly valid at the time of the Sharp disclosure on July 6, 2000. Thus, viewed in light of the state of the art, the disclosure of Sharp would not have conveyed to the skilled artisan the specific idea of producing PPCA in an insect cell for the purpose of producing a pharmaceutical composition useful for treating Galactosialidosis. This idea is only apparent from the application disclosure which is the subject of this appeal.

D. Conclusion

The specification sufficiently describes the claimed pharmaceutical compositions and enables one of ordinary skill in the art to make and use these compositions without undue experimentation. Furthermore, the Sharp reference fails to anticipate the claimed invention because it fails to teach a composition comprising a protein produced in an insect cell culture that is useful for treating a lysosomal storage disorder. Reversal of all outstanding rejections against pending claims 8-13 for the reasons set forth herein and in Appellant's prior responses is therefore respectfully requested.

Respectfully submitted,



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APPENDIX OF CLAIMS INVOLVED IN THIS APPEAL

8. A pharmaceutical composition comprising a protein useful for treating a lysosomal storage disorder other than Fabry disease that is selectively imported into macrophages when administered to a subject and a pharmaceutically acceptable carrier, wherein said protein is produced in an insect cell culture.

9. The composition of claim 8 wherein said lysosomal storage disorder is Galactosialidosis.

10. The composition of claim 8 wherein said protein is protective protein/cathepsin A (PPCA).

11 The composition of claim 8 wherein said insect cell culture comprises cells derived from the species selected from the group consisting of *Spodoptera frugiperda* and *Tricoplusia ni.*

12 The composition of claim 11 wherein said cells are *Spodoptera frugiperda* Sf9 cells.

13 The composition of claim 8 wherein said protein is produced in the cell culture using a baculovirus expression system.